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Effectiveness and safety of a paclitaxel-eluting stent for superficial femoral artery lesions up to 190 mm: One-year outcomes of the single-arm IMPERIAL long lesion sub-study of the Eluvia drug-eluting stent

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Keywords:	Drug-eluting stent, Superficial femoral artery, Peripheral artery disease, Paclitaxel, Lesion length
Abstract:	Purpose: Report the clinical effect of femoropopliteal artery treatment with a drug-eluting stent in patients with long lesions. Methods: The global IMPERIAL Long Lesion sub-study is a prospective single-arm, multicenter trial of the Eluvia Drug-Eluting Vascular Stent System (Boston Scientific, Marlborough, MA, USA) for treating femoropopliteal artery lesions >140 mm and ≤190 mm in length. Primary patency (duplex ultrasound PSVR ≤2.4 in the absence of clinically-driven target lesion revascularization or bypass of the target lesion) and major adverse events (e.g., all causes of death through 1 month, target limb major amputation through 12 months, or target lesion revascularization through 12 months) were assessed at 12 months. Results: Fifty patients (mean age 68.2 years, 64% men) with mean lesion length 162.8 ± 34.7 mm were enrolled (40% with diabetes, 28% with severe calcification, 32% with occlusion). At 12 months, the Kaplan-Meier estimate of primary patency was 87.9% and 93.5% of patients were free from major adverse events. No stent thrombosis was observed and no target limb amputations were performed. Conclusions: Results from the IMPERIAL Long Lesion sub-study demonstrate excellent patency and safety through 1 year among patients with long femoropopliteal occlusive disease treated with the Eluvia stent.

JEVT-19-0350 Responses2Comments

Reviewer Comments to the Author:

Reviewer: 1

Thank you for submitting this paper, which demonstrates the efficacy of Eluvia stent in "long" lesions. Here are my comments:

1. [...]Stent diameters of 6 mm and 7 mm and lengths of 40-150 mm were available for use in the study. Use of overlapping stents was expected to cover the entire lesion length [...]: It is well known that a number of physicians faced problems with the initial 200mm device. Have you used these devices in this trial and if yes, have you excluded them?

Response: Eluvia was never available in 200mm lengths, but the reviewer may be referring to the 150mm length which is not currently available commercially. The study was enrolled while the 150mm length was commercially available in Europe, and patients treated with that length (36 of 94 total stents implanted) are included in the analysis as noted in the Procedures section of the Results. No unanticipated adverse device events were reported in the study (with any length).

2. [...] dual antiplatelet therapy for the first 60 days post-procedure, and antiplatelet monotherapy through 12-month follow-up [...]: What did you recommend in patients on oral anticoagulation?

Response: Patients on anticoagulation for comorbid conditions could be exempted from antiplatelet requirements if the addition of dual-antiplatelet therapy posed an intolerable bleeding risk in the opinion of the treating investigator. This protocol detail has been added to the revised text (page 5, last paragraph).

3. Why did you stop recruitment at 50 pts? I find this number a big limitation considering that you have recruited pts from 24 centres, i.e. 2 pts per centre.

Response: As stated in the Statistical Analysis section of the Methods, "The Long Lesion sub-study was exploratory, and the sample size was not determined statistically." Sample size of 50 patients was specified in the study protocol prior to commencing enrollment. This number was not statistically-driven, but was chosen to provide descriptive information regarding Eluvia performance in lesions longer than those allowed in the RCT portion of the IMPERIAL study. The enrollment distribution was uneven across centers.

4. Based on the current recommendations of ESC/ESVS guidelines 16 mm is not a long lesion anymore. It is, of course, longer than the lesions of the RCT but still not comparable to the studies regarding other

devices. I would rephrase the title because at the current form it is misleading: Eluvia is safe in long lesions (for the reader a long lesion is also 200 and 250 mm as well).

Response: The title has been revised to specify the lesion length inclusion criteria; however, IMPERIAL "Long Lesion Substudy" is the name of the study as registered (clinicaltrials.gov NCT02574481) so we have not changed the subtitle portion that names the study.

The sub-study objective statement has been revised to reduce emphasis on "long lesions" (page 4, first paragraph), and the Methods section now clarifies the desire to assess overlapping stent use (page 5, first paragraph). Although other types of study designs have previously included lengths >200 mm, pivotal trials for FDA device approval have not. We also wanted to avoid including TASCII D lesions, which guidelines recommend treating with surgery.

The Discussion has been amended to emphasize the study objective of assessing overlapping device performance in a structured trial setting, which necessitated constraining the number of overlapping stents to be implanted and therefore the maximum lesion length; and to clarify limitations of generalizing the results to all "long" lesions (page 12, paragraph 2).

5. [...] The duplex ultrasound imaging finding observed in 4 patients was not associated with clinical sequelae, but the evolution of this phenomenon will be further assessed via transverse duplex ultrasound evaluations to be performed at future follow up visits. [...]: What kind of finding is that? I cannot find it in the Results section.

Response: Please see the response to comment 8.

6. [...] A retrospective single center review of Zilver PTX for long lesions reported 1-year restenosis >50% (based on duplex ultrasound peak systolic velocity ratio) for 19% of patients with lesions 20 cm or shorter (mean 13.9 cm) and 40% for patients with lesions longer than 20 cm (mean 33.0 cm) [...]: This is what I mean with my previous comment. You cannot compare the results of your study with the results of ZilverPTX study in lesions of 33cm. How should we call those lesions: ultralong? You have to be more precise in your title.

Response: We agree that the <20 cm (mean 13.9 cm) subcohort from the Zilver PTX study is likely a better comparator than the >20 cm subcohort with mean length of 33 cm. Since neither group perfectly matches the IMPERIAL study cohort, and other unaccounted-for patient characteristics or study differences will also affect patient outcomes, we included both in the Discussion to provide a range of lesion lengths and corresponding restenosis rates for reference. We have revised the start of this paragraph to clarify that the referenced results are intended to provide a contextual range of expected efficacy, not direct comparisons with the IMPERIAL study results (page 11, paragraph 2).

7. [...] Results from the IMPERIAL Long Lesion sub-study demonstrate excellent treatment durability and safety through 1 year among patients with long femoropopliteal occlusive disease treated with the

Eluvia stent [...]: The right description would be instead of long to write ... among patients with 140-190 mm fem pop disease.

Response: The Conclusion has been revised as suggested.

8. In the study from Bisdas et al and in the IMPERIAL trial there were some concerns about positive remodeling / aneurysmatic degenaration of the aneurysm wall. Have you seen similar problems in your cohort?

Response: The ultrasound imaging finding described by Bisdas et al was observed in 4 patients enrolled in this cohort; these 4 were included in the number reported previously by Gray et al for the overall study. Clarifying information has been added to the Results (page 9, paragraph 3).

Reviewer: 2

In his study authors report the clinical effect of femoropopliteal artery treatment with a drug-eluting stent in patients with long lesions. This substudy is a prospective single-arm, multicenter trial of the Eluvia Drug-Eluting Vascular Stent System for treating femoropopliteal artery lesions >140 mm and ≤190 mm in length.

9. I cannot understand why they limited the length to 190 mm, so the average around 160 mm is in the gray zone. I would call enrolled lesions as intermediate lesion instead than long lesions. i think this is the major limitation of the study. authors should explain this.

Response: Please see the response to Comment 4. In addition, the inclusion criterion of maximum length 190mm was based on visual assessment by the treating investigator; subsequent core lab analysis showed that lesion lengths actually ranged up to about 244 mm, with a median length of 180 mm (page 8, paragraph 1).

10. Population enrolled is 50 patients. How did they calculate the number?

Response: Please see the response to comment 3.

11. I would suggest to present the primary patency and other endpoints at 12 months and within the follow-up window time (30 or 60 days).

Response: The follow up window was 12 months ± 30 days. The observed primary patency (87.0%) and TLR (6.5%) rates account for evaluations within this window. The Kaplan-Meier estimate of patency is shown through 13 months in Figure 2A.

12. In the discussion section they compared studies that treated long lesions. They should acknowledge this, so probably a shorter and more focused discussion could be better.

Response: We acknowledge the limited comparability between the reported study and previous studies due to differences in eligibility criteria and other factors. We have revised the Discussion to clarify that the referenced results are intended to provide a contextual range of expected efficacy, not direct comparisons with the IMPERIAL study results. The Discussion has also been amended to clarify limitations of generalizing the results to all "long" lesions (page 11, paragraph 2; page 12 paragraph 2).

Effectiveness and safety of a paclitaxel-eluting stent for ~~long~~ superficial femoral artery lesions up to 190 mm: One-year outcomes of the single-arm IMPERIAL long lesion sub-study of the Eluvia drug-eluting stent

Commented [DE1]: Comment 4

Abstract

Purpose

Report the clinical effect of femoropopliteal artery treatment with a drug-eluting stent in patients with long lesions.

Methods

The global IMPERIAL Long Lesion sub-study is a prospective single-arm, multicenter trial of the Eluvia Drug-Eluting Vascular Stent System (Boston Scientific, Marlborough, MA, USA) for treating femoropopliteal artery lesions >140 mm and ≤190 mm in length. Primary patency (duplex ultrasound PSVR ≤2.4 in the absence of clinically-driven target lesion revascularization or bypass of the target lesion) and major adverse events (e.g., all causes of death through 1 month, target limb major amputation through 12 months, or target lesion revascularization through 12 months) were assessed at 12 months.

Results

Fifty patients (mean age 68.2 years, 64% men) with mean lesion length 162.8 ± 34.7 mm were enrolled (40% with diabetes, 28% with severe calcification, 32% with occlusion). At 12 months, the Kaplan-Meier estimate of primary patency was 87.9% and 93.5% of patients were free from

major adverse events. No stent thrombosis was observed and no target limb amputations were performed.

Conclusions

Results from the IMPERIAL Long Lesion sub-study demonstrate excellent patency and safety through 1 year among patients with long femoropopliteal occlusive disease treated with the Eluvia stent.

Clinical trial registration: ClinicalTrials.gov, identifier NCT02574481.

Key words: drug-eluting stent, paclitaxel, peripheral arterial disease

Introduction

Endovascular treatment with angioplasty or bare-metal stenting of obstructive lesions in the superficial femoral artery (SFA) or proximal popliteal artery (PPA) is commonly practiced to alleviate symptoms of claudication or critical limb ischemia. However, restenosis of the treated lesion occurs at an unsatisfactory rate and may necessitate reintervention. Drug-coated and drug-eluting therapies including stents and balloons have been developed with the aim of reducing reintervention rates by preventing restenosis. Complex (i.e., long, calcified, occluded) lesions commonly occur in the SFA/PPA segment and a significant number of patients who receive primary balloon angioplasty require a stent.[1-4] Consequently, benefits of drug-eluting stents have been hypothesized for the femoropopliteal segment, particularly for complex lesions, but effects have not yet been clearly established.

Prospective clinical trial data on drug-eluting stent use in the SFA/PPA segment is gradually accumulating. The antirestenotic effect of a paclitaxel-coated stent compared with non-drug coated treatment was demonstrated in the Zilver PTX RCT[5] and single arm studies.[6] These were followed by the MAJESTIC first-in-human[7] and the IMPERIAL randomized head-to-head studies of the paclitaxel-eluting Eluvia stent.[8] Superior primary patency for Eluvia over Zilver PTX at one year was demonstrated in the randomized controlled trial, but in relatively short to moderate lesion lengths (mean lesion lengths of 81.8 mm and 86.5 mm for the Zilver PTX and Eluvia arms, respectively). Mean lesion length was even shorter in the Zilver PTX RCT[9] comparing Zilver PTX with bare metal stents (approximately 65 mm) and only approximately 100 mm in the single arm study.[6]

To address the scarcity of available clinical trial data regarding drug-eluting stent effectiveness in patients with long lesions, a ~~Long Lesion~~ sub-study was conducted under the auspices of the

global IMPERIAL trial. The sub-study objective was to evaluate the safety and effectiveness of overlapping ~~the~~ Eluvia Drug-Eluting Vascular Stents ~~System~~ for treating ~~long-length~~ SFA lesions longer than those eligible for the randomized trial.

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Methods

Study Design

The IMPERIAL trial includes 3 parts: the primary randomized trial, a pharmacokinetic sub-study, and a prospective single-arm study of patients with long lesions. Primary results from the randomized study and the pharmacokinetic sub-study were published previously.[8] Clinical sites participating in the randomized or pharmacokinetic IMPERIAL studies could also enroll patients in the single-arm, non-blinded Long Lesion sub-study. All patients in the non-randomized Long Lesion sub-study were treated with the Eluvia Vascular Stent System (Boston Scientific, Marlborough, MA, USA).

The Institutional Review Board, Independent Ethics Committee, or Research Ethics Board applicable to each study site provided ethical approval for the study protocol. Patients provided written informed consent to participate in the study. The lead author and study principal investigators had full access to the data in the study and take responsibility for its integrity and the data analysis. This trial is registered with ClinicalTrials.gov, identifier NCT02574481.

The data and study protocol for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

Participants

Patient eligibility criteria for the IMPERIAL Long Lesion sub-study were identical to those applied in the randomized study[8] with the exception of lesion length. Briefly, adults at least 18 years of age with symptomatic lower limb ischemia (Rutherford category 2, 3, or 4) and stenotic or occlusive lesions in the native SFA or PPA, stenosis of ≥70% (visual angiographic assessment), and vessel diameter ≥4mm and ≤6mm were eligible. Total lesion length >140 mm and ≤190 mm (visual angiographic assessment) was required for inclusion in the Long Lesion sub-study; patients with lesions ≤140 mm could be enrolled in the randomized study. The eligible range of 140 to 190 mm was determined by the objective of assessing performance of two overlapping Eluvia stents to cover the entire stent length in accordance with the device Directions for Use (i.e., with 5 mm stent overlap and 5 mm extension into healthy tissue). Targeting lesions ≤190 mm (ie, TASCII D) also aligned with contemporary recommendations for endovascular rather than surgical treatment.[10]

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Procedures

The self-expanding nitinol Eluvia Stent is coated with a biostable polymer (poly vinylidene fluoride-co-hexafluoropropylene) and paclitaxel at a dose density of 0.167 µg paclitaxel per mm^2 stent surface area. Stent diameters of 6 mm and 7 mm and lengths of 40-150 mm were available for use in the study. Use of two overlapping stents was expected to cover the entire lesion length.

Commented [DE4]: Comment 4

At a minimum, anticoagulation and antiplatelet therapy required clopidogrel or ticlopidine starting at least 24 hours prior to the procedure or a peri-procedural loading dose, dual antiplatelet therapy for the first 60 days post-procedure, and antiplatelet monotherapy through 12-month follow-up. Antiplatelet monotherapy was recommended through trial completion at 5 years. Patients on anticoagulation for comorbid conditions could be exempted from antiplatelet

requirements if, in the opinion of the treating investigator, the addition of dual-antiplatelet therapy posed an intolerable bleeding risk.

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Endpoints and Follow-up

The primary effectiveness endpoint was 12-month (± 30 days) primary patency. Primary vessel patency was defined as duplex ultrasound peak systolic velocity ratio ≤ 2.4 as assessed by a core laboratory (VasCore, Boston, MA, USA), in the absence of clinically-driven target lesion revascularization (TLR) or bypass of the target lesion. Clinically-driven TLR was defined as a reintervention within 5 mm proximal or distal to the original treatment segment for ≥50% angiographic diameter stenosis in the presence of recurrent symptoms (≥ 1 change in Rutherford class) or associated with decreased ankle-brachial index of ≥20% or ≥ 0.15 in the treated segment.

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The primary safety endpoint was 12-month freedom from major adverse events (MAEs), defined as all causes of death through 1 month, target limb major amputation through 12 months, or TLR through 12 months. A Clinical Events Committee adjudicated all deaths, amputations, TLRs, and stent thrombosis.

Procedural success was defined as technical success (ie, delivery and deployment of the assigned study stent to the target lesion with residual angiographic stenosis no greater than 30% as assessed by the implanting investigator) with no MAEs within 24 hours of the index procedure.

Twelve-month follow-up included stent integrity, clinical outcome, and health-related quality of life assessments. Radiographs obtained at the 12-month visit were evaluated by an independent core laboratory (VasCore, Boston, MA, USA). Possible fractures were verified by comparison with procedural angiography by the angiographic core laboratory (Beth Israel Deaconess

Medical Center, Boston, MA, USA). Clinical improvement was assessed with Rutherford categorization and walking function was evaluated with the Walking Impairment Questionnaire (WIQ) and 6-minute walk test. Hemodynamic improvement was defined as an ankle-brachial index (ABI) increase by ≥ 0.1 as compared with the pre-procedure value or to an ABI ≥ 0.90, without TLR. General health status was assessed with the EQ-5D questionnaire. Hospitalizations associated with TLR, target vessel revascularization, or procedure- or device-related adverse events were counted through 1 year post-procedure.

Statistical Analysis

The Long Lesion sub-study was exploratory, and the sample size was not determined statistically. For the primary effectiveness endpoint assessment, the observed primary patency rate was compared with a non-statistically based performance goal of 60%. The performance goal was determined by adding 10% (estimated drug effect) to the historical patency rate for long lengths of the bare nitinol stent platform.[11]

No hypothesis testing was performed for the primary safety endpoint, but the MAE-free rate was expected to be similar to that reported at 12 months for the IMPERIAL randomized study (i.e., 95%).[8]

Categorical variables are reported as counts and percentages and continuous variables are reported as mean (SD). The Kaplan-Meier product-limit method was used to estimate the time-to-event-free rates for primary patency and freedom from TLR. Paired t-tests were used to compare follow-up outcome scores with baseline values; a p value of less than 0.05 indicated statistical significance. Analyses were performed with Statistical Analysis Software (SAS), version 9.2 or later (SAS Institute Inc., Cary, North Carolina).

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Comment 10

Results

Patients

A total of 50 patients at 24 IMPERIAL clinical sites in Austria, Belgium, Japan, New Zealand, and the USA were enrolled in the Long Lesion sub-study. Patient baseline characteristics are summarized in Table 1. Forty percent of patients had diabetes and 32% were current smokers. As determined by the angiographic core laboratory, mean lesion length was 162.8±34.7 mm (median 180 mm, interquartile range 160-190 mm), 70% had moderately or severely calcified lesions, and 32% had occlusions. No deaths occurred during 12 months of follow-up and one patient withdrew from the study (Figure 1).

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Procedures

A total of 94 stents were implanted in the 50 patients (mean of 1.9 stents per patient). Sixty two percent (58/94) of stents were lengths of 40-120 mm and the remainder were 150 mm in length. Balloon predilatation was performed in 88% (44/50) of patients. The procedure success rate was 98% (49/50); residual stenosis >30% was reported by the investigative site for one patient and no MAEs were reported within 24 hours of the procedures.

Dual antiplatelet therapy was reported for 84% (42/50) of patients at both discharge and 1 month post-procedure. Acetylsalicylic acid use was reported by 89% (40/45) of patients at 12 months, with dual antiplatelet therapy continuing for 73.3% (33/45).

Effectiveness and Safety

The observed primary patency rate was 87.0% at 12 months (Table 2), which exceeded the performance goal. The Kaplan-Meier estimate of primary patency was 87.9% at 12 months (Figure 2).

The MAE-free rate at 12 months was 93.5% (Table 2) due to 3 TLR procedures. All TLRs were considered clinically-driven. No deaths occurred through 12 months. No stent thrombosis was observed and no target limb amputations were performed.

Among patients in the Long Lesion sub-study with suitable ultrasound imaging (transverse ultrasound imaging was not systematically performed for all patients), the ultrasound core laboratory identified 4 patients with a suspected localized inflammatory response characterized by a hypoechoic halo around the stent. These 4 cases from the Long Lesion cohort were included in the number reported previously for the overall study.[12] All 4 patients' stents were patent and none had a stent thrombosis or TLR through one year.

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One patient with two stents had radiographically and angiographically-confirmed fracture in both stents, both were grade V mid-stent fractures.[13] Both stents were patent at 12-month follow up with no associated complications or adverse events.

Clinical Outcomes and Hospitalization

A total of 91.5% (43/47) of patients had Rutherford category improvement without the need for TLR and 87.2% (41/47) were classified as Rutherford category 0 or 1 at 12 months (Figure 3). Hemodynamic improvement (i.e., ABI improvement without reintervention) was observed in 82.2% (37/45) of patients.

Walking function improved from baseline, with the overall WIQ score improving from 49.48±28.94 at baseline to 80.32±24.97 ($p<0.0001$) at 12 months in addition to significantly

improved distance, speed, and stair climbing scores (Table 3). Walking distance and speed also increased based on the 6-minute walk test, with mean distance walked increasing from 240.0±147.8 m to 293.5±123.8 m and speed increasing from 44.2 ±21.9 m/min to 50.3 ±19.3 m/min (p=0.009).

Although average EQ-5D health-related quality of life index scores remained consistent over the course of the study, the proportions of patients reporting "no problems" related to mobility, usual activities, and pain increased after treatment (Table 4).

No patients required inpatient hospitalization due to TLR, TVR, or procedure- or device-related adverse events during 12-month follow-up.

Discussion

A 12-month primary patency rate of 88.5% (Kaplan-Meier estimate) and MAE rate of 4.9% was previously shown for patients who were treated with Eluvia in the IMPERIAL RCT (mean lesion length 86.5 mm).[8] Results of the IMPERIAL Long Lesion sub-study, which enrolled a separate set of patients with mean lesion length approximately double that of the RCT (162.8 mm), were remarkably similar at 1 year, with a primary patency rate of 87.9% and MAE rate of 6.5%. Although the Long Lesion sub-study had a relatively small sample size, the results suggest that 1-year patency with the Eluvia drug-eluting stent was independent of lesion length. These consistent results were observed despite the presence of additional factors generally associated with poorer patency outcomes, such as calcified lesions (moderate or severe in 70% of patients) and occlusions (present in 32% of patients), which are also more representative of real-world clinical populations. No significant safety events occurred. The duplex ultrasound imaging

finding observed in 4 patients was not associated with clinical sequelae, but the evolution of this phenomenon will be further assessed via transverse duplex ultrasound evaluations to be performed at future follow up visits.

~~These results compare favorably with~~Comparisons with previous ~~previous~~ studies of paclitaxel-~~eluting~~ stent use ~~in long lesions.~~ are limited due to differences across clinical studies, including lesion length inclusion criteria and other baseline characteristics. However, these studies provide a range of reference and context for the IMPERIAL study results. In a registry of Eluvia use at a single European center, a 12-month primary patency rate of 87% in patients with a mean lesion length of 20 cm (48% with critical limb ischemia) was reported,[14] further supporting the notion of independence between patency and lesion length for patients treated with Eluvia. Treatment of long lesions with the paclitaxel-coated Zilver PTX stent yielded 1-year primary patency rates of 52.5% in a single-center registry in France (mean lesion length 25 cm, 51% with critical limb ischemia at baseline)[15] and 86.4% in a multicenter registry in Japan (mean lesion length 14.7 cm, 21.5% with critical limb ischemia).[16] A retrospective single center review of Zilver PTX for long lesions[17] reported 1-year restenosis >50% (based on duplex ultrasound peak systolic velocity ratio) for 19% of patients with lesions 20 cm or shorter (mean 13.9 cm) and 40% for patients with lesions longer than 20 cm (mean 33.0 cm). More long-term follow-up data are needed to evaluate the benefits of drug-eluting stents for long lesions, particularly in comparison with drug-coated balloon treatment.

Drug-coated balloon treatment is easily customized to lesion length, but stand-alone use in long femoropopliteal lesions has not demonstrated durability over time. Treatment with the In.Pact paclitaxel-coated balloon resulted in 1-year patency rates of 76-83% (reported primary patency or binary restenosis) across three studies with mean lesion lengths ranging from 19-25 cm.[2-4] At

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2 years, the reported patency rates declined to 54% and 70%.[2,3] Treatment with the Lutonix paclitaxel-coated balloon likewise showed a steep decline in patency among patients with long lesions (mean length 21 cm) in the Lutonix Global SFA Registry; by 2 years the patency rate was 67%.[1] Drug-coated balloon treatment was compared with Zilver PTX drug-coated stent treatment in the randomized 150-patient REAL-PTX pilot study.[18] Study results suggested a non-significant advantage for the stent only after 2 and 3 years, with the differential effect most pronounced among patients with lesions longer than 10 cm.[18] These preliminary observations are limited by the very small sample size with long lesions and long term follow-up in the pilot study. Whether drug-eluting stent treatment proves to overcome the limitations of drug-coated balloon treatment in long femoropopliteal segment lesions over time remains to be seen.

Limitations of the IMPERIAL Long Lesion sub-study include the short duration of follow-up to date. Follow-up is ongoing and duplex ultrasound patency assessments will be repeated at 2 years and at the final 5-year follow-up visit. The lesion length inclusion criteria were "long" relative to the randomized portion of the IMPERIAL trial, which included lengths less than 140 mm, but were constrained to a maximum of 190 mm in order to assess performance of two overlapping stents in a structured trial setting. The range of 140 to 190 mm as defined by the inclusion criteria yielded a mean length of 162.8 mm by core lab assessment, which may not be considered "long" according to current guidelines,[19] and the study results may not be generalizable to lesions longer than those studied here. The study does not directly address possible advantages of long, single stent placement compared with stent overlap when two or more stents are implanted. The single-arm, non-comparative design as well as the relatively small number of treated patients also limit the generalizability of the study results.

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Comment 12

Conclusion

Results from the IMPERIAL Long Lesion sub-study demonstrate excellent treatment durability and safety through 1 year among patients with ~~long~~ femoropopliteal occlusive disease up to 190 cm long treated with the Eluvia stent.

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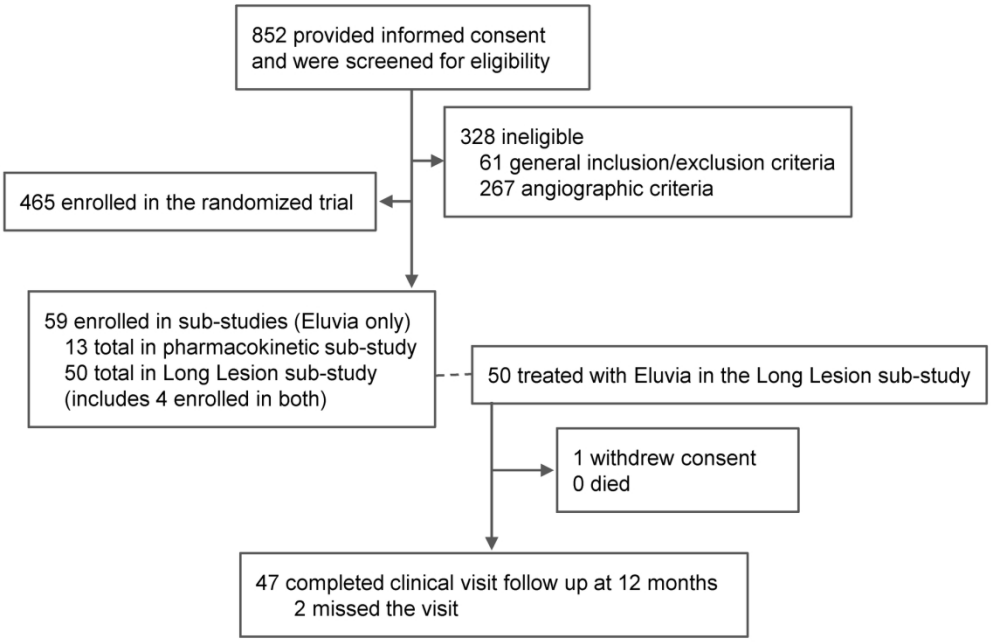
Figure Legends

Figure 1. Patient flow

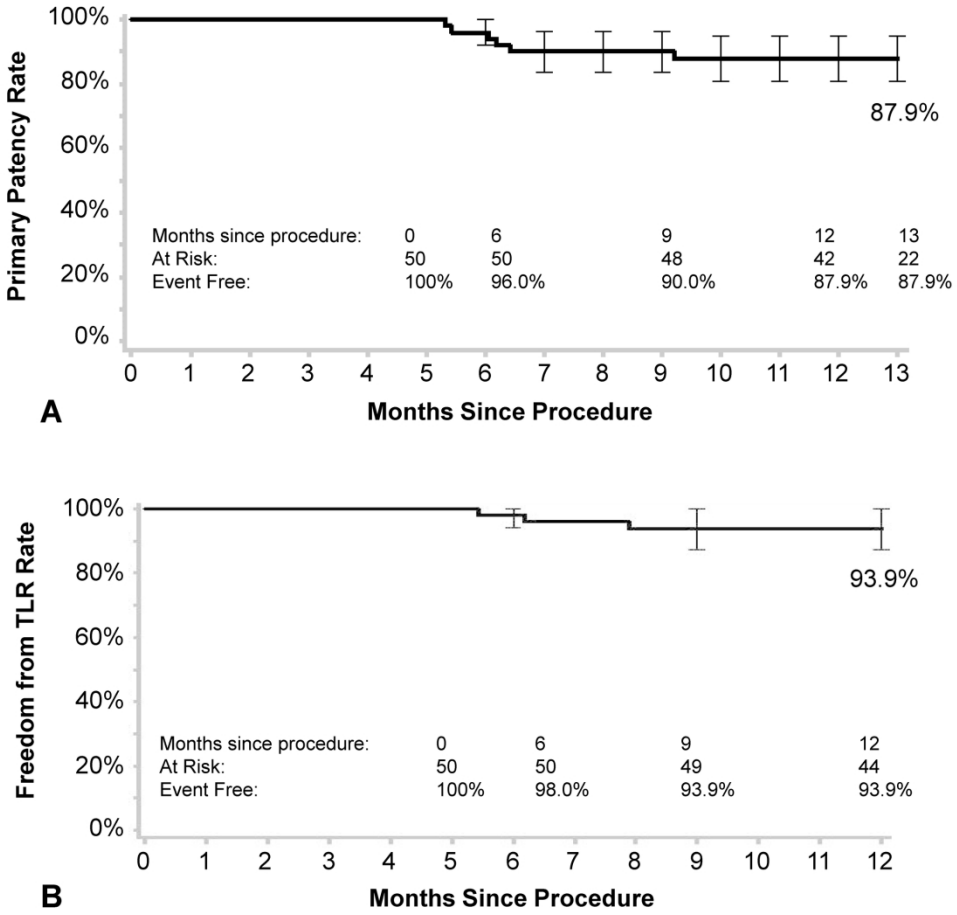
Figure 2. Kaplan-Meier estimate of primary patency (A) and target lesion revascularization (B), with standard errors.

Figure 3. Rutherford category distribution



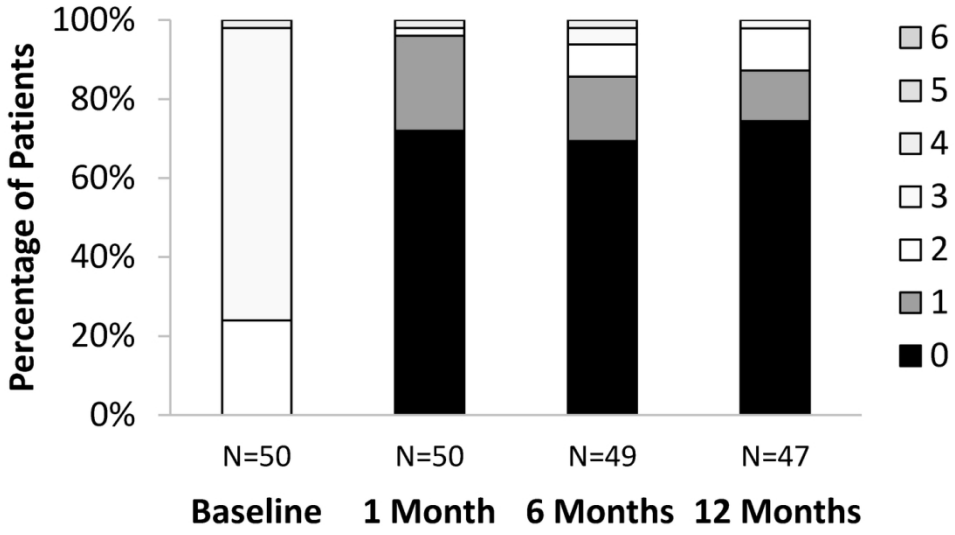
Patient flow

163x108mm (300 x 300 DPI)



Kaplan-Meier estimate of primary patency (A) and target lesion revascularization (B), with standard errors.

202x186mm (300 x 300 DPI)



Rutherford category distribution

131x74mm (300 x 300 DPI)

Table 1. Baseline patient and lesion characteristics

Characteristic	N=50
Age (years)	68.2±8.9
Male sex	64.0% (32)
Race or ethnicity	
Hispanic or Latino	6.0% (3)
Caucasian	60.0% (30)
Asian	22.0% (11)
Black, or African heritage	12.0% (6)
Smoking status	
Current	32.0% (16)
Previous	52.0% (26)
Diabetes mellitus	40.0% (20)
Type 1	5.0% (1)
Type 2	90.0% (18)
Unknown	5.0% (1)
Hyperlipidemia	82.0% (41)
Hypertension	92.0% (46)
Coronary artery disease	56.0% (28)
Myocardial infarction	18.0% (9)
Congestive heart failure	16.0% (8)
Renal insufficiency	6.0% (3)
Angiographic Characteristics[a]	

Arterial Segments[b]	
Ostial	2.0% (1)
Proximal	54.0% (27)
Mid	90.0% (45)
Distal (including proximal popliteal)	76.0% (38)
Length (mm)[c]	162.8±34.7
Reference vessel diameter (mm)	4.7±0.7
Calcification[d]	
None/Mild	28.0% (14)
Moderate	42.0% (21)
Severe	28.0% (14)
Unknown	2.0% (1)
% Diameter Stenosis	81.9%±15.0%
<50%	2.0% (1)
50%-99%	66.0% (33)
100% (Occlusion)	32.0% (16)
Ankle brachial index	0.7±0.2

Mean ± SD or % (n).

[a]Angiographic characteristics are based on core laboratory assessment.

[b]More than one arterial segment per patient was allowed.

[c]Inclusion criterion was based on operator assessment of lesion length; lesion length was subsequently assessed by the core laboratory.

[d]Calcification was assessed by the core laboratory. Moderate calcification defined as radiopacities noted on one side of the arterial wall or less than one cm of length prior to contrast injection or digital subtraction. Severe calcification defined as radiopacities noted on both sides of the arterial wall and extending more than 1 cm of length prior to contrast injection or digital subtraction.

Table 2. Efficacy and safety results

	Event Rate
Primary patency[a]	87.0% (40/46)
MAE-free	93.5% (43/46)
MAE	6.5% (3/46)
All-cause death at 1 month	0.0% (0/46)
Target limb major amputation	0.0% (0/46)
Target lesion revascularization	6.5% (3/46)
Stent thrombosis	0.0% (0/46)
All-cause death through 12 months	0.0% (0/46)

MAE, major adverse event.

[a]Percentage of target stented segments with duplex ultrasound peak systolic velocity ratio ≤ 2.4, in the absence of clinically-driven target lesion revascularization or bypass of the target lesion.

Table 3. Walking Impairment Questionnaire (WIQ) results

	Baseline	1 Month	6 Months	12 Months
N	48	50	48	47
Distance	32.16±30.05	57.90±34.54	64.21±35.27	58.67±36.60
Change from Baseline		26.95±32.66	31.80±41.90	26.45±35.34
p		<0.001	<0.001	<0.001
Speed	28.44±23.06	40.15±22.85	43.66±27.14	41.21±25.95
Change from Baseline		12.93±28.17	15.31±33.28	11.50±30.94
p		0.003	0.003	0.017
Stair Climbing	35.85±30.68	60.00±32.59	56.77±33.25	56.29±34.55
Change from Baseline		25.17±31.09	20.20±43.32	18.33±38.44
p		<0.001	0.003	0.003
Walking Impairment	49.48±28.94	83.00±24.45	86.46±17.83	80.32±24.97
Change from Baseline		32.81±35.04	36.41±34.84	31.11±35.42
p		<0.001	<0.001	<0.001

Values reported as mean ± SD. P values from paired t-test.

Table 4. EQ-5D Health Status

	Baseline	1 Month	6 Months	12 Months
N	48	50	48	47
EQ-5D Dimension[a]				
Mobility				
No problems	10.4% (5)	46.0% (23)	39.6% (19)	44.7% (21)
Slight problems	25.0% (12)	32.0% (16)	37.5% (18)	21.3% (10)
Moderate problems	43.8% (21)	16.0% (8)	18.8% (9)	21.3% (10)
Severe problems	20.8% (10)	6.0% (3)	4.2% (2)	12.8% (6)
Unable	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Personal Care				
No problems	93.8% (45)	96.0% (48)	93.8% (45)	87.2% (41)
Slight problems	6.3% (3)	2.0% (1)	4.2% (2)	4.3% (2)
Moderate problems	0.0% (0)	0.0% (0)	0.0% (0)	6.4% (3)
Severe problems	0.0% (0)	2.0% (1)	2.1% (1)	2.1% (1)
Unable	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Usual Activities				
No problems	45.8% (22)	60.0% (30)	72.9% (35)	72.3% (34)
Slight problems	29.2% (14)	30.0% (15)	12.5% (6)	12.8% (6)
Moderate problems	16.7% (8)	10.0% (5)	10.4% (5)	12.8% (6)
Severe problems	6.3% (3)	0.0% (0)	4.2% (2)	2.1% (1)
Unable	2.1% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Pain/ Discomfort				

None	16.7% (8)	42.0% (21)	50.0% (24)	46.8% (22)
Slight	33.3% (16)	36.0% (18)	37.5% (18)	31.9% (15)
Moderate	29.2% (14)	12.0% (6)	10.4% (5)	14.9% (7)
Severe	20.8% (10)	10.0% (5)	2.1% (1)	4.3% (2)
Extreme	0.0% (0)	0.0% (0)	0.0% (0)	2.1% (1)
Anxiety/ Depression				
None	66.7% (32)	74.0% (37)	70.8% (34)	72.3% (34)
Slight	22.9% (11)	16.0% (8)	25.0% (12)	21.3% (10)
Moderate	8.3% (4)	6.0% (3)	4.2% (2)	6.4% (3)
Severe	2.1% (1)	4.0% (2)	0.0% (0)	0.0% (0)
Extreme	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Summary Index[b]	0.8±0.1	0.8±0.1	0.8±0.1	0.8±0.1
Visual Analogue Scale[c]	67.5±18.5	75.4±16.4	74.4±17.2	70.6±20.6

[a]Values reported as % (n) of patients reporting problems with each dimension.

[b]Summary index values calculated based on the United States value set; reported as mean ± SD.

[c]Visual Analogue Scale (VAS) ranged from 0 (worst imaginable health state) to 100 (best imaginable health state); reported as mean ± SD.